## REMARKS

Claims 1, 26, 28, and 53 are pending in the present application.

Claims 2-25, 27, and 29-52 have been cancelled without prejudice.

Claims 1, 28, and 53 are amended to specify that the cytokine is a CCL21 cytokine and to specify that the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut. Support for these amendments can be found in the specification, e.g., at page 4, lines 2-6; page 7, lines 14-25; page 9, lines 13-17; page 17, lines 19-25; in Examples 1-8 on pages 31-37, in Examples 14-19 on pages 40-47; and in original claims 27 and 28.

No new matter is introduced by these amendments.

**Prior Rejections.**

Applicants gratefully acknowledge that the prior written description, anticipation and obviousness rejections have been withdrawn.

**Rejections Under the First Paragraph of 35 U.S.C. §112.**

Claims 1, 26, 28, and 53 stand rejected under the first paragraph of 35 U.S.C. §112, as allegedly failing to comply with the enablement requirement. According to the Office Action, the specification is enabling for a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier, but is not enabling for such a DNA vaccine in which the cytokine can be any cytokine. The claims are now amended to specify that the cytokine is a CCL21 cytokine, rendering this rejection moot. It should be noted that claims 28 and 53 were already directed to DNA constructs in which the cytokine was a CCL21 cytokine (i.e., SEQ ID NO: 7). Since these claims have already been searched, there is no impediment to the entry of the present amendments. Reconsideration and withdrawal of this rejection is requested.

**Rejections Under 35 U.S.C. §103(a).**

Claims 1, 26, 28, and 53 stand rejected as allegedly being obvious under 35 U.S.C. §103(a) over the combination of Rovero *et al.* taken with Altieri *et al.*, Nagira *et al.*, Bennett *et al.*, and Tanabe *et al.*, and claims 1 and 28 in further combination with Pawelek *et al.* with respect to incorporation of the DNA construct into an attenuated *Salmonella typhimurium* vector. These rejections are unwarranted.

According to the Office Action, it would have been obvious to one of ordinary skill in the art to have replaced the DNA encoding Her-2/neu antigen of the Rovero vaccine with DNA encoding survivin, based on the teachings of Altieri *et al.* and Bennett *et al.* (i.e., that survivin is a desirable target for anti-cancer therapy). The Office Action also asserts that one of ordinary skill in the art would have been motivated to replace the IL-1β DNA of the Rovero vaccine with CCL21 DNA, based on the teachings of Nagira *et al.* and Tanabe *et al.* regarding the immune stimulating ability of CCL21 for attracting B and T cells, and that one of ordinary skill in the art would have been motivated to incorporate the so-modified Rovero vaccine in an attenuated *Salmonella typhimurium* vector based on the teachings of Pawelek *et al.* In other words, it would have been obvious to replace every feature of the primary reference with different components, leaving nothing of the original Rovero vaccine intact! Applicants submit that such a complete rebuilding of the vaccine evidences inventive activity rather than the routine, non-inventive act of one of ordinary skill in the art.

The principal reference, Rovero *et al.*, discloses a plasmid DNA vaccine encoding the tumor antigen Her-2/neu and an immunologically active fragment of IL-1β. The reference reports that immunization with this vaccine elicited lymphocyte infiltration into the stroma surrounding the terminal ductal-lobular units (TDLU) and induction of antibodies against the Her-2/neu antigen (anti-p185neu), and delayed tumor appearance in mice, but did not induce significant cytotoxic T lymphocyte (CTL) response (see page 449, col. 2, last full paragraph). Rovero *et al.* also reported that a plasmid DNA encoding only the Her-2/neu antigen did not elicit any significant immune response in the same mouse model (*Id.*).

In contrast, the presently claimed vaccine does indeed elicit activation of CTLs (i.e., CD8 T cells). The present application indicates that while a vaccine encoding only the survivin protein did induce some anti-tumor response, the claimed combination encoding both survivin and CCL21 was significantly more effective (see in particular the results described in

Examples 4, 5, and 17, on pages 33-35 and 44-45, demonstrating significant CD8 T cell activation in mice treated with the claimed vaccines, and Examples 3, 8, and 15, on pages 31-33, 36-37, and 41-43). These results show that the presently claimed vaccines indeed operate by a significantly different immunological mechanism, i.e., via cellular immunity (CTL activation). The vaccines of Rovero *et al.* on the other hand, appear to invoke only humoral immunity (antibody production), a different immunological mechanism.

Antibody production via B cells and cytotoxic T lymphocyte activation are very different and complex mechanisms (see Lauren Sompayrac, *How the Immune System Works*, 2nd Ed., Blackwell Publishing, Malden, MA, 2003, pages 71-72, a copy of which is attached hereto in Appendix A, for a concise discussion of the differences between antibody immune response and CTL responses). For example, B cell produces antibodies that bind to specific antigens. A B cell recognizes an antigen in its "natural state" (e.g., a full length protein) that has been "opsinized" by complement (part of the innate immune system). In contrast, a CTL recognizes an antigen that has been chopped up and is presented to the CTL as small fragments bound to MHC class I molecules on cell surfaces. Each of these mechanisms invokes different receptors. Each of these mechanisms also requires stimulation from different biochemical signals (e.g., different types of cytokines and different types of helper cells).

The anti-cancer art is relatively unpredictable. The present Office Action has acknowledged that in the enablement rejection. The DNA vaccines of the present invention can be characterized as a novel form of "gene therapy" in that the vaccine must transfect antigen presenting cells (APC) in order to elicit an immune response. The U.S. Patent and Trademark Office has also recognized that gene therapy is an unpredictable art (see for example, the presentation on Gene Therapy by Supervisory Patent Examiner Karen M. Hauda, Art Group Unit 1632, found at the USPTO website, a copy of which is attached hereto in Appendix B).

The immune system is indeed complex and unpredictable. In order to be effective, immune system cells (e.g., B cells, Th cells, and/or CTLs) must migrate to, and infiltrate the tumor cite. Prior art of record, such as Altieri *et al.* and Nagira *et al.*, while providing general statements about the utility of a particular antigen or cytokine, provide little more than an invitation to experiment, but do not provide to one of ordinary skill a reasonable

expectation that modifying a vaccine such as that of Rovero *et al.* by replacing the antigen target as well as the immunostimulating cytokine would be successful. This is particularly evident in the present case, where more than one factor is being altered in the primary reference at the same time, and the mechanism of the immune response is dramatically different.

Regarding claims 1 and 28, Pawelek *et al.* disclose different *Salmonella typhimurium* strains. The Pawelek *et al.* strains have been selected to be super-infective toward tumor cells (see col. 7, lines 50-65, and col. 31-39, Examples 7.2, 8, and 9, which describe the isolation of super-infective, tumor-specific *Salmonella typhimurium*). In contrast, the presently claimed vaccines utilize attenuated *Salmonella typhimurium* that target the Peyer's patches in the gut, rather than tumor cells directly. One of ordinary skill in the art would not have been motivated to incorporate the hypothesized, highly modified Rovero vaccine (i.e., comprising DNA encoding survivin and CCL21), into an attenuated *Salmonella typhimurium* that targets Peyer's patches, based on the disclosure in Pawelek *et al.* regarding different *Salmonella typhimurium* strains, which are super-infective and which target tumor cells. Accordingly, a *prima facie* case for obviousness has not been established.

In a desperate but failed attempt to show a *prima facie* case of obviousness, the Examiner cites Applicants' own teachings out of context. In the Office Action at page 21, the Examiner relies on Applicants' own teachings. In the passage cited by the Examiner at page 4, lines 3-6 of the Specification (not page 2, paragraph [0013]) Applicants are referring to attenuated *S. typhimurium* strains that target Peyer's patches, not to the Pawelek, *et al.* strains said to be super-infective toward tumor cells.

On page 20 of the present Office Action, the Examiner seeks to characterize the Field of the Invention based on Pawelek *et al.* That is improper. The pertinent field in the present case, at the very least, is DNA vaccines as stated by the Applicants on page 1, lines 14-20 of the present application.

The Examiner's own, unsupported contention that one of ordinary skill in the art would have been motivated to use the claimed attenuated *S. typhimurium* strains because other, different *S. typhimurium* strains are super-infective and tumor specific is a *non sequitur*, and cannot support a rejection in any event. Reliance on the Examiner's own expertise also is improper. The rejection must be based on the record, which is not the case here.

To establish a *prima facie* case of obviousness it remains necessary to identify a valid reason that would have led one of ordinary skill in the pertinent art to depart from the express teachings of the prior art references, and to modify those teachings in the particular manner taught by the applicants. The present record does not show that. Rejections on obviousness grounds cannot be sustained by mere conclusory statements. *KRS Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (No. 04-1350, decided April 30, 2007), citing with approval *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

**Conclusion.**

In view of the foregoing claim amendments and the accompanying discussion, Applicants request reconsideration, allowance of the present claims, and early passage of the application to issue. In the event the foregoing is deemed to be unpersuasive, Applicants request that this amendment be entered to place the claims in better form for appeal.

Respectfully submitted,

Dated 30 July 2007 By _____

Talivaldis Cepuritis (Reg. No. 20,818)

OLSON & HIERL, LTD.
20 North Wacker Drive
36th Floor
Chicago, Illinois 60606
(312) 580-1180

Application No. 10/807,897

## APPENDIX A

Copies of the title page, copyright page, and pages 71-72 of Lauren Sompayrac, *How the Immune System Works*, 2nd Ed., Blackwell Publishing, Malden, MA, 2003, are attached on the following pages.

# HOW THE IMMUNE SYSTEM WORKS, *2ND Edition*

LAUREN SOMPAYRAC, PhD

Retired Professor
Department of Molecular, Cellular, and Developmental Biology
University of Colorado
Boulder, Colorado

**Blackwell**
Publishing

Blackwell Publishing, Inc., 350 Main Street, Malden, Massachusetts 02148-5018, USA
Blackwell Science Ltd, Osney Mead, Oxford OX2 0EL, UK
Blackwell Science Asia Pty Ltd, 550 Swanston Street, Carlton South, Victoria 3053, Australia
Blackwell Verlag GmbH, Kurfürstendamm 57, 10707 Berlin, Germany



04 05 06 6 5 4 3

ISBN: 0-632-04702-X

Library of Congress Cataloging-in-Publication Data

Sompayrac, Lauren.
How the immune system works / Lauren Sompayrac. – 2nd ed.
p. ; cm.
Includes index.
ISBN 0-632-04702-X
1. Immune system. 2. Immunity. I. Title.
[DNLM: 1. Immune System–physiology. 2. Immune System –anatomy & histology. 3. Immune System–physiopathology. 4. Immunity–physiology. QW 504 S697h 2003]
QR181.S65 2003
616.07'9–dc21

2002014141

A catalogue record for this title is available from the British Library

Acquisitions: Nancy Anastasi Duffy
Development: Amy Nuttbrock
Production: Debra Lally
Cover design: Meral Dabcovich
Typesetter: SNP Best-set Typesetter Ltd., Hong Kong
Printed and bound by Edwards Bros. in Ann Arbor, MI

For further information on Blackwell Publishing, visit our website:
www.medirect.com

# LYMPHOID ORGANS AND LYMPHOCYTE TRAFFICKING

## REVIEW

I'm sure you noticed during the last lecture that there are many similarities between T cells and B cells. As a way of reviewing, let's recall some of the ways that T and B cells are similar – and different.

BCRs and TCRs both have "recognition" proteins that extend outside the cell, and which are incredibly diverse because they are made by a strategy of mixing and matching gene segments. For the BCR, these are the light and heavy chains that make up the antibody molecule. For the TCR, the molecules that recognize antigen are the α and β or γ and δ proteins. TCRs and BCRs have cytoplasmic tails that are too short to signal recognition, so additional molecules are required for this purpose. For the BCR, these signaling proteins are called Igα and Igβ, while for the TCR, signaling involves a complex of proteins called CD3.

For B and T cells to be activated, their receptors must be clustered by antigen, because this crosslinking brings together many of their signaling molecules in a small region of the cell. When the density of signaling molecules is great enough, an enzymatic chain reaction is set off that conveys the "receptor engaged" signal to the cell's nucleus. There, in the "brain center" of the cell, genes involved in activation are turned off or on as a result of this signal. Although crosslinking of receptors is essential for activation, it is not enough. Naive B and T cells also require co-stimulatory signals that are not antigen specific. For B cell activation, a helper T cell can provide co-stimulation through surface proteins called CD40L that plug into CD40 proteins on the B cell surface. For T cells, one form of co-stimulation involves B7 proteins on an antigen presenting cell that engage CD28 proteins on the surface of the T cell.

In addition to recognition and signaling molecules, BCRs and TCRs also associate with co-receptor molecules that serve to amplify the signal that the receptors send. For B cells, this co-receptor is one which recognizes antigen that has been opsonized by complement. If the BCR recognizes an antigen, and if that antigen is also "decorated" with complement protein fragments, the antigen serves as a "clamp" that brings the BCR and the complement receptor together on the surface of the B cell, greatly amplifying the "receptor engaged" signal. As a consequence, B cells are much more easily activated (many fewer BCRs must be crosslinked) by antigen that has been opsonized by complement.

T cells also have co-receptors: Th cells express CD4 molecules on their surfaces, and CTLs express CD8 molecules. When a TCR binds to antigen presented by MHC proteins, the co-receptor molecule on the T cell surface also binds to the MHC molecule. This serves to amplify the signal that is sent by the TCR to the nucleus, so that the T cell is more easily activated (fewer TCRs must be crosslinked). Of course, these co-receptors only work with the "right" MHC types: class I for CTLs with CD8 co-receptors and class II for Th cells with CD4 co-receptors.

So co-receptors are really "focus" molecules. The B cell co-receptor helps B cells focus on antigens that have already been identified by the complement system as dangerous (those that have been opsonized). The CD4 co-receptor focuses the attention of Th cells on antigens displayed by class II MHC molecules, and the CD8 co-receptor focuses CTLs on antigens displayed by class I MHC molecules.

When B and T cells are activated, growth factor receptors appear on their surfaces. This allows them to proliferate in response to the appropriate growth factors, and to form a clone of cells that has the same

antigen specificity. B and Th cells are also similar in that when they are re-stimulated, they get a chance to change the molecules they secrete. B cells can undergo class switching to produce IgG, IgA, or IgE antibodies in place of the default antibody class, IgM. Helper T cells can secrete a whole list of cytokines in addition to, or instead of, the default cytokine IL-2. For B cells, the change in antibody class is influenced by cytokines present in the local environment when the decision to change classes is made. For helper T cells, the decision to produce certain cytokines is determined both by the type of co-stimulation the Th cell receives and by the cytokine milieu.

There are also important differences between B cells and T cells. The BCR recognizes antigen in its "natural" state – that is, antigen that has not been chopped up and bound to MHC molecules. This antigen can be a protein or almost any other organic molecule (e.g., a carbohydrate or a fat). In contrast, the αβ receptors on a T cell only recognize fragments of proteins that are presented by MHC molecules. So the BCR has much greater variety in the type of antigen it can recognize. However, because the TCR looks at small fragments of proteins, it can recognize targets that are hidden from view of the BCR in an intact and tightly folded protein.

Of course, B and T cells have different functions. B cells secrete antibodies – a non-membrane-anchored form of the BCR. In contrast, the TCR stays firmly anchored on the surface of the T cell. Experienced B cells can function as antigen presenting cells, but T cells cannot. CTLs are killers, but B cells do not kill. Finally, Th cells are major cytokine producers, whereas B cells usually produce cytokines only in small amounts.

During an infection, the parts of the rearranged heavy and light chain genes that specify the antigen binding region of the B cell receptor can undergo somatic hypermutation and selection. As a result, the average affinity of the collection of BCRs increases. So in a sense, B cells can "draw from the deck" to try to get a better hand. In contrast, the TCR does not hypermutate, so T cells must be satisfied with the cards they are dealt. B cells are produced more or less continuously throughout the lifetime of a human, but the production of virgin T cells decreases as a person ages. The reason is that the organ in which T cells mature, the thymus, steadily decreases in activity after puberty, so fewer and fewer freshly minted T cells roll off the thymic assembly line as we get older. That's one reason why some viral diseases such as mumps, which are just a nuisance to a kid, can be deadly serious to an older person.

Certainly one of the most elegant features of the immune system is the way Mother Nature arranges to "let the punishment fit the crime." Dendritic antigen presenting cells observe the battle first hand, and the intelligence they gather there is complete enough to allow them to formulate a "game plan." Once activated, dendritic cells travel to nearby lymph nodes, where they activate T cells. During this process, the game plan is conveyed to T cells in the form of co-stimulatory molecules (including cytokines) that are expressed by the dendritic cells. This information instructs helper T cells which cytokines to make to defend against a particular invader, and informs both Th cells and CTLs where in the body they should travel to join in the fight. In a sense, the dendritic cell functions as the "coach" of the immune system team, while the Th cell performs the duties of "quarterback" by calling the plays designed by the coach. It is important to note that the cell that functions as coach is actually part of the innate immune system. So the innate system determines not only when the adaptive system should be activated in response to danger, but also instructs the adaptive system on which weapons to deploy and where to send them.

## SECONDARY LYMPHOID ORGANS AND LYMPHOCYTE TRAFFICKING

Up to this point, we've discussed the various elements of innate and adaptive immunity, and how they interact to make an integrated defense "system." However, to really understand how the immune system works, one must have a clear picture of where in the body all these interactions take place. So in this lecture, we're going to focus on the "geography" of the immune system.

The immune system's defense against an invader

Application No. 10/807,897

**APPENDIX B**

Copies of slides from the Patent Office Presentation on Gene therapy by Supervisory Patent Examiner Karen M. Hauda, Art Group Unit 1632, from the USPTO website are attached on the following pages.

## Gene Therapy: Overcoming Enablement Rejections

UNITED STATES PATENT AND TRADEMARK OFFICE

**Karen M. Hauda**
**Supervisory Patent Examiner**
**Art Unit 1632**
**(703) 305-6608**
**karen.hauda@uspto.gov**

## Gene Therapy and Transgenic Animals

SPE Art Unit 1632
Karen M. Hauda
(703) 305-6608
karen.hauda@uspto.gov

SPE Art Unit 1633
Deborah J. Clark
(703) 305-4051
deborah.clark@uspto.gov

## Overview

- What is Gene Therapy
- Utility Issues
- Written Description Issues
- Enablement Issues

## Gene Therapy

- Traditionally
  - Replacement of a defective gene
- Currently– Delivery of a Polynucleotide
  - Replacement of a defective gene
  - Vaccine treatment
  - DNA immunization
  - Anti-sense therapy (Art Unit 1635)

## Gene Therapy

- Cancer
- Skin Disorders
- Vascular Disease
- Cardiac Disease
- Auto-immune Disease
- Blood Disorders
- Parasitic Infections
- Viral Infections
- Bacterial Infections
- Yeast Infections
- Neurological Disease
- Hereditary Diseases

## Modes of "Gene Therapy"

- "Disease Treatment"

  - *In vivo*
    - Direct introduction of nucleic acid into host
  - *Ex vivo*
    - Introduction of transduced/transfected cells

## Utility Issues

- Typically Uncommon
- Examiner Must Make *Prima Facie* Case
- Usually Resolved by Rewording Claim
  - Original claim:
    - Method of preventing or curing HIV infection
  - Modified to:
    - Method of treating HIV infection

## Written Description Issues

- Might Apply Depending on the Breadth of the Claim
- Consider:
  - The scope of the polynucleotide construct
  - The scope of the therapeutic gene
  - If the polynucleotide lacks written description, the method of using the polynucleotide will also lack written description

## Enablement

- More Often an Issue
- **However**, Gene Therapy Has Progressed Dramatically in the Past 5 Years

## Gene Therapy Is Unpredictable

- 2008- Gomez-Navarro. Eur. J. of Cancer, Vol. 35:867-885.
- 1999- Clay et al. Path. Onc. Res., Vol. 5:3-15.
- 1999- Palu et al. J. of Biotechnology, Vol. 68:1-13.
- 1998- Anderson. Nature, Vol. 392:25-30.
- 1997- Verma et al. Nature, Vol. 389:239-242.
- 1995- Crystal. Science, Vol. 270: 404-410.
- 1995- Miller et al. FASEB J., Vol. 9:190-199.
- 1994- Culver. TIG, Vol. 10: 174-178.
- 1993- Mulligan. Science, Vol. 260: 926-932.
- 1992- Roemer et al. Eur. J. Biochem., Vol. 208:211-255.
- 1990- Miller. Blood, Vol. 76: 271-278.

## Obstacles for Gene Therapy

- Stable Expression of Encoded Gene
- Host Immune Responses to Vectors
- Targeting Vectors to Specific Cells
- Specificity of Vector Expression
- Representative Animal Models
- Recognition of Immunogenic Epitopes which Provide a Therapeutic Benefit

## Why It Matters:

- "The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed."

In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).

## Gene Therapy Claims

- Examination Considerations
  - Sufficient administration
  - Sufficient expression
  - Art recognition of animal model
  - Phenotypic change correlated to the disease

## Examiner Analysis of Gene Therapy Claims

- EVALUATE CLAIMS ON:
  - Scope of the vector
    - (adenoviral, retroviral, naked DNA, liposomes)
  - Scope of delivery
    - (IM, IV, Sub Q, ID, Oral, tissue specific target)
  - Scope of treatment
    - (cancer, vaccine, viruses, hereditary, etc.)
  - Scope of antigens
    - (related to disease being treated?)
  - Potential for ineffective *in vivo* responses
    - (against vector, against cells, against host)

## Examiner Analysis of Gene Therapy Claims

- EVALUATE WHAT IS DISCLOSED
  - Working examples in the specification
  - Teachings of unpredictable parameters
  - Predictability of the art for the claimed scope
  - Correlation of working examples to the claimed invention
  - Correlation of working examples in the prior art to the claimed invention
  - Correlation of animal model to disease

## We DO NOT Require Clinical Data

## Gene Therapy Is Unpredictable, But Particular Embodiments ARE Patentable

## Gene Therapy Patents

- Over 1034 Gene Therapy Patents Issued
  - 1994 — 3 Issued
  - 1995 — 6 Issued
  - 1996 — 21 Issued
  - 1997 — 89 Issued
  - 1998 — 133 Issued
  - 1999 — 167 Issued
  - 2000 — 374 Issued
  - 2001 — 241 Issued (as of July)

## When Drafting a Claim

- Consider:
  - What is the invention?
    - Vector?
    - Mode of administration?
    - Therapeutic?
  - What is disclosed?
    - Therapeutic?
    - "Tool" for introducing nucleic acids?

## TIP – Scope of the Claim

- The Scope of the Claim Should be Commensurate with the Enabled Disclosure.
  - Ex. Delivery of DNA for treatment
    - (consider limiting disease, vector, route of delivery)
  - Ex. Delivery of DNA for producing Ab
    - (consider claiming "A method for producing Ab...")

## TIP – Claim Construction

- Provide Claims Directed to the Inventive Concept

- Provide Evidence Based Upon the Nature of the Invention
  - Delivery, therapy, cellular targeting, etc.

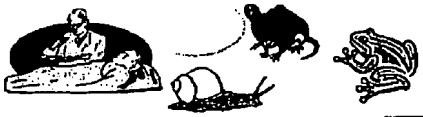
## TIP – Consider Other Uses

- **A composition only needs one enabled use**
- When Claiming a Composition
  - Consider whether the composition can be used for purposes other than Therapy
  - Include these uses in the description of the specification

## Gene Therapy and Transgenic Animals

SPE Art Unit 1632
Karen M. Hauda
(703) 305-6608
karen.hauda@uspto.gov

SPE Art Unit 1633
Deborah J. Clark
(703) 305-4051
deborah.clark@uspto.gov



## Gene Therapy: Overcoming Enablement Rejections

UNITED STATES PATENT AND TRADEMARK OFFICE

**Karen M. Hauda**
**Supervisory Patent Examiner**
**Art Unit 1632**
**(703) 305-6608**
**karen.hauda@uspto.gov**